REMARKS

I. Preliminary Comments

The present invention is directed to methods for treating patients with therapeutic adenovirus compositions. Those methods comprise carrying out the first step of a) preparing a therapeutic adenovirus composition by a process that includes i) growing host cells in a media; ii) providing nutrients to said host cells; iii) infecting said host cells with an adenovirus; iv) lysing said host cells to provide a lysate; v) purifying adenovirus from said lysate to provide therapeutic adenovirus; vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition; and a second step b) of administering the therapeutic adenovirus composition to a patient.

Claims 70, 101, 132, 163 and 194 have been amended to recite that the method includes the step of preparing an adenovirus composition by a process including steps i-iv.

Claims 71, 102, 133, 164 and 195 have been amended in order to provide antecedent basis for the recitation of "the starting PFU" by specifying that it is the starting PFU of the lysate of step iv. This recitation is supported by the disclosure as originally presented and introduces no new matter.

II. The Outstanding Rejections

Claims 70-226 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 12 and 31 of Zhang et al., U.S. Patent 6,726,907.

Claims 70-226 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31 and 33-37 of Zhang, Copending Application No. 09/203,078 (US 2004/0229335 A1).

Claims 70-226 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More specifically, claims 71, 102, 133, 164 and 195 stand rejected as lacking antecedent basis for the limitation "the starting PFU." Claims 78, 109, 140, 171 and 202 stand rejected on the basis that the metes and bounds of the recitation "below the detection level of a western blot assay" are unclear.

Claims 70-226 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Claims 70-226 stand rejected under 35 U.S.C. §112, first paragraph as failing to provide an enabling disclosure.

Claims 70-226 stand rejected under 35 U.S.C. §102(e) over Zhang U.S. 6,410,010.

Claims 73-74, 77, 104-105, 108, 135-136, 139, 166-167, 170, 197-198 and 201 stand rejected under 35 U.S.C. §103(a) over Zhang U.S. 6,410,010 and Shabram, U.S. 5,837,520.

III. Patentability Arguments

A. The Obviousness-type Double Patenting Rejection Should be Withdrawn.

The rejection of claims 70-226 under the judicially created doctrine of obviousness-type double patenting over claims 12 and 31 of Zhang et al., U.S. 6,726,907 should be withdrawn because the present claims are directed to treatment of a patient which is patentably distinct from claims 12 and 31 of Zhang which recite purified adenovirus compositions. Claims 12 and 31 of Zhang fail to teach the methods of the application claims which are directed to treatment methods. Accordingly, the obviousness-type double patenting rejection should be withdrawn.

B. The Provisional Double Patenting Rejection Should be Deferred.

The provisional rejection of claims 70-226 under the judicially created doctrine of obviousness-type double patenting over Zhang et al., Copending Application No. 09/203,078 (US 2004/0229335 A1) should be deferred because the pending claims in that case have not yet been patented. Accordingly, it is not necessary to take any action with respect to them at this time.

C. The Indefiniteness Rejection Under 35 U.S.C. §112 (Second Paragraph) Should be Withdrawn.

The indefiniteness rejection of claims 70-226 under U.S.C. §112 (second paragraph) should be withdrawn because the claims do recite "a positive step of treatment" and are readily understood by those of skill in the art. Specifically, the claims recite a method comprising the sub-steps of (a) preparing a therapeutic virus composition by a process including specified steps and (b) administering the composition to a patient. These steps are positive steps of treatment and no further recitation is required for those of skill in the art to understand whether one would or would not practice the claims of the invention. Similarly,

the claims are sufficiently definite so that an examination may be carried out and it may readily be determined whether any prior art reference or activity would read upon the subject matter of the claims.

Accordingly, the rejection under 35 U.S.C. §112 (second paragraph) should be withdrawn.

D. The Indefiniteness Rejection of Claims 71, 102, 133, 164 and 195 Should be Withdrawn.

The rejection of claims 71, 102, 133, 164 and 195 as lacking antecedent basis for the limitation "the starting PFU" should be withdrawn in light of the amendment of each of those claims wherein antecedent basis is now provided. Accordingly, the rejection under 35 U.S.C. §112 (second paragraph) should be withdrawn.

E. The Indefiniteness Rejection of Claims 78, 109, 140, 171 and 202 Should be Withdrawn.

The rejection of claims 78, 109, 140, 171 and 202 should be withdrawn because the metes and bounds of the recitation "below the detection level of a western blot assay" are clear and would be understood by those of ordinary skill in the art. The definiteness requirement of 35 U.S.C. §112 (second paragraph) exists to ensure that those practicing in the general field of the invention know whether their activities are encompassed by the claims or are not. Western Blot analysis is widely practiced and is well known to the art and no evidence or logic has been presented that would suggest that those of ordinary skill in the art would not recognize what is encompassed by the recitation of "a BSA content below the detection level of a western blot assay." Specifically, Fig. 13 of the disclosure depicts a western blot assay in which the BSA present in purified virus was below the detection level of the western blot assay.

Moreover, similar language has been accepted by the Patent and Trademark Office and is present in claim 10 of co-owned Zhang et al., Patent U.S. 6,726,907 (a copy of which is attached hereto as Appendix A). Finally, similar language directed to undetectable levels of a component when measured by Western Blot analysis was also issued in Lynch et al., U.S. 5,118,606 (a copy of which is attached hereto as Appendix B, see claim 15 and claims 18 and 27 depending therefrom.) Accordingly, the rejection under 35 U.S.C. §112 (second paragraph) should be withdrawn.

F. The Rejections for Lack of Written Description Should be Withdrawn.

The rejections of claims 20-226 for lack of written description under 35 U.S.C. §112 (first paragraph) should be withdrawn because the claims serve as their own written description and they make clear that the inventors were in possession of the invention so claimed at the time their application was filed. (See *In re Koller*, 204 USPQ 702 (CCPA 1980)) Applicants describe their invention throughout their disclosure and teach its practice in a manner such that those of ordinary skill would recognize that Applicants were in possession of the invention claimed.

The "essential goal" of the written description requirement is to clearly convey that "an applicant has invented the subject matter which is claimed" (*In re Barker*, 194 USPQ 470, 473 (CCPA 1977) cited in MPEP 2163) and no reasons have been set forth why one of ordinary skill would not believe that applicants were in possession of their originally claimed invention at the time of filing. In contrast with the lack of rationale why those of ordinary skill would not believe Applicants were in possession of the invention described in their claims, there is a "strong presumption" that an adequate written description is present in the specification as filed (MPEP 2163 II A citing *In re Wertheim* 191 USPQ 90, 96 (CCPA 1976)). The MPEP further states that "the rejection of an original claim for lack of written description should be rare."

The rejection that no support exists for genus claims because "no adenoviruses have been disclosed that are therapeutic in and of themselves" is improper because the specification makes clear that the adenoviral vectors can encode exogenous gene constructs with therapeutic activities. As such, the encoded antisense and therapeutic gene constructs can be therapeutic as opposed to the adenoviral vectors themselves. Moreover, as acknowledged by the Examiner, the specification teaches a wide variety of species of different aspects of the invention including different promoters and a variety of therapeutic genes, antisense genes and antigen genes. Because the present invention is directed to an improved method of obtaining and purifying adenovirus in order to obtain a therapeutic composition, the species and structure of species of therapeutic gene comprised by the virus are irrelevant to this aspect of the invention and there is no requirement that these species of the genera be distinguished.

To the extent that the issues raised in the outstanding "written description" rejection are really issues relating to the enablement requirement of Section 112 (first paragraph) the Examiner's attention is directed to the later discussion directed to those issues.

G. The Rejections for Lack of Enablement Should be Withdrawn.

The rejections for lack of enablement should be withdrawn because the specification provides ample direction to practice the claimed invention beyond just treatment of cancer by direct administration of an adenoviral vector encoding wild-type p53. With respect to this rejection, the claimed invention is generally directed to "A method of treating a patient with a therapeutic adenovirus composition" which preparation has been prepared by a particular process. The Examiner acknowledges that the specification is enabling for "a method of treating cancer in a patient comprising a direct administration of an adenoviral vector, which vector comprises a promoter operably linked to a nucleotide sequence encoding wild-type p53, which administration causes the transformation of cancer cells and expression of such p53 transgene, thereby inhibiting the uncontrolled growth of the cancer..."

The specification is enabling beyond just methods of treating cancer and beyond gene therapy by direct administration of an adenoviral vector. The specification teaches treatment of cancer by administration of adenoviral vectors comprising therapeutic genes other than p53 and teaches administration by a variety of modes. In addition, the specification teaches treatment of non-cancer diseases by administration of a variety of therapeutic genes.

"The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 Fed. Cir. 1993)). Applicants respectfully note that "it is incumbent upon the Patent Office... to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.05 (quoting *In re Marszocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). As will be discussed below, the reasons expressed in the Action fail to cast doubt as to the sufficiency of the present disclosure to allow a person of ordinary skill in the art to practice the invention without undue experimentation. There is no reason why a person could not take the disclosure and practice the invention as claimed in claims 70-226.

Accordingly, the specification teaches how to make and use the claimed invention, and thus, it enables claims 70-226.

While the Action argues that gene therapy is difficult and unpredictable and that these unpredictabilities have not yet been overcome by the art Applicants point out that the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marszocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971) With respect to those specific contentions, the Action provides no such evidence to challenge the specification's assertion that a method of treatment would be effected. For example, the specification teaches that tumor cells may be treated and the claims do not limit tumor cells to those lacking p53. This must be taken at face value unless the Action can point to evidence that undermines this assertion.

With respect to cancer treatment, there are references that indicate the invention will work as claimed; these references indicate that tumor cells carrying a wild-type p53 gene are susceptible to p53 gene therapy. For example, the reference of Hamada *et al.* Cancer Research 56: 3047-3054 (1996) (Appendix C) shows that a number of p53-positive cervical cell lines -HeLa, C4-I, MS751, ME180, CaSki, and SiHa-are amenable to p53 gene therapy using adenovirus. This reference addresses the issue of whether cancers with mutations unrelated to p53 may be treated by the claimed invention. Thus, contrary to the unsupported assertion in the Action, there is no reason to doubt the invention will work as claimed with respect to cancer. Further, the specification teaches that other disease conditions may be treated by adenoviral administration of other therapeutic genes. As discussed below, the specification teaches treatment of adenosine deaminase deficiency, human blood clotting factor IX deficiency in hemophilia B, cystic fibrosis, involving the replacement of the cystic fibrosis transmembrane receptor gene as well as treatment of hyperproliferative disorders such as rheumatoid arthritis or restenosis by transfer of genes encoding angiogenesis inhibitors or cell cycle inhibitors.

The Action urges that Applicants review the references Deonarain, Verma, Eck et al., Gorecki and Green to show that gene therapy is unpredictable. First, these references only generalize about gene therapy. More importantly, none of the references state that gene therapy will not work and is a complete failure. Instead, they focus on more clinical issues, which are above and beyond the standards for patentability. See *In re Krimmel*, 292 F.2d

948, 954 (C.C.P.A. 1961) ("There is nothing in the patent stature or any other statues...which give the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming, and which he has state are useful for 'pharmaceutical applications,' are safe, effective, and reliable for use with humans.").

Deonarain identifies the issues of targeting genes to sufficient populations of cells and of adequate expression but does not state that gene therapy will not work. In fact, Applicants' own evidence and that of others demonstrates (and the Examiner accepts) that gene therapy does work with respect to the p53 gene and cancer. Accordingly, the issues raised by Dornarain do not indicate that the specification is defective in any way.

The text of the Verma reference makes no comment about Ad-p53 cancer therapy that would suggest that the claims are not enabled. Applicants emphasize that the claims are directed to Ad-p53 cancer therapy and other gene therapies, which the specification teaches, and this reference does not indict the disclosure in any way. For example, the reference does not say that practicing cancer or other gene therapies according to the claims would require undue experimentation. Accordingly, Applicants submit that the Verma reference is not dispositive on the issue of enablement.

Similarly, the Eck reference identifies a number of factors important to gene therapy but does not suggest that those of skill in the art would be unequipped to address such factors in a gene therapy protocol. Gorecki addresses similar issues of stability and of expression levels but does not state that such are obstacles which are insurmountable to those of ordinary skill in the art.

Finally, the Action contrasts the identification by Green of key hurdles to be overcome for effective gene therapy with adenoviral vectors and cancer with the disclosure of Zhang U.S. 6,740,320 which describes those very hurdles being overcome in the use of p53-encoding adenoviruses for treating cancer in animals. This being the case, there exists no reason to doubt the enablement of the claimed invention by Applicants' specification.

Applicants further note that there are other scientific articles that rebut any contention that intravenous or systemic delivery of adenovirus vectors will not work. The article of Nemunaitis et al. Gene Therapy 8:746-759 (2001) (Appendix D) indicates that "intravenous administration of genetically altered adenovirus is a feasible approach." In Nemunaitis et al., the authors report their findings from a dose-escalation clinical trial involving patients with different cancers and they confirmed intratumoral delivery and replication of the adenovirus.

See Nemunaitis et al. at 749, Table 1, and Fig. 3 and 4. In another article Shiriwawa et al., Cancer Gene Therapy 5 (5): 274-280 (1998) (Appendix E) mice were treated for osteosarcoma pulmonary metastasis using an intravenously administered adenovirus containing a thymidine kinase gene. Accordingly, the Action's contention that alternative delivery methods are problematic is rebutted.

The specification provides a teaching that allows a person of ordinary skill in the art to practice the invention without undue experimentation, and none of the references cited by the Action provide evidence that the invention will not work as described and claimed. More particularly, Applicants' disclosure provides examples of diseases other than cancer for which the viral vectors of the invention would be useful including, but not limited to, adenosine deaminase deficiency, human blood clotting factor IX deficiency in hemophilia B, and cystic fibrosis, which would involve the replacement of the cystic fibrosis transmembrane receptor gene. The disclosure also teaches vectors that could be used for treatment of hyperproliferative disorders such as rheumatoid arthritis or restenosis by transfer of genes encoding angiogenesis inhibitors or cell cycle inhibitors. The specification further teaches that transfer of prodrug activators such as the HSV-TK gene could be used in the treatment of hyperproliferative disorders, including cancer. (Page 47, line 25 through page 48, line 3)

Applicants' disclosure also teaches the use of adenoviral vectors comprising genes encoding enzymes such as cytosine deaminase, hypoxanthine-guanine phosphoribosyl-transferase, galactose-l-phosphate uridyltransferase, phenylalanine hydroxylase, glucocerbrosidase, sphingomyelinase, alpha-L-iduronidase, glucose-6-phosphate dehydrogenase, HSV thymidine kinase and human thymidine kinase. (Page 46, line 27 through page 47, line 2) The specification further teaches adenoviral vectors comprising genes encoding hormones including growth hormone, prolactin, placental lactogen, luteinizing hormone, follicle-stimulating hormone, chorionic gonadotropin, thyroid-stimulating hormone, leptin, adrenocorticotropin (ACTH), angiotensin I and II, beta-endorphin, beta-melanocyte stimulating hormone (beta-MSH), cholecystokinin, endothelin I, galanin, gastric inhibitory peptide (GIP), glucagon, insulin, lipotropins, neurophysins, somatostatin, calcitonin, calcitonin gene related peptide (CGRP), beta-calcitonin gene related peptide, hypercalcemia of malignancy factor (1-40), parathyroid hormone-related protein (107-139) (PTH-rP), parathyroid hormone-related protein (107-111) (PTH-rP), glucagon-like peptide (GLP-1), pancreastatin, pancreatic peptide, peptide YY, PHM, secretin, vasoactive

intestinal peptide (VIP), oxytocin, vasopressin (AVP), vasotocin, enkephalinamide, metorphinamide, alpha melanocyte stimulating hormone (alpha-MSH), atrial natriuretic factor (5-28) (ANF), amylin, amyloid P component (SAP-1), corticotropin releasing hormone (CRH), growth hormone releasing factor (GHRH), luteinizing hormone-releasing hormone (LHRH), neuropeptide Y, substance K (neurokinin A), substance P and thyrotropin releasing hormone (TRH). Also disclosed by the specification is the use of adenoviral vectors comprising genes encoding interleukins and cytokines including Interleukin 1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF and G-CSF. (Page 47, lines 4-23)

The specification also teaches the use of the adenoviral vectors as vaccines for the administration of genes encoding antigens such as viral antigens, bacterial antigens, fungal antigens or parasitic antigens. Such antigens are disclosed to include those from viruses such as picomavirus, coronavirus, togavirus, flavirviru, rhabdovirus, paramyxovirus, orthomyxovirus, bunyavirus, arenvirus, reovirus, retrovirus, papovavirus, parvovirus, herpesvirus, poxvirus, hepadnavirus, and spongiform virus. Preferred viral targets include influenza, herpes simplex virus 1 and 2, measles, small pox, polio or HIV. Pathogens include trypanosomes, tapeworms, roundworms, helminths. Genes encoding other antigens include those encoding tumor markers, such as fetal antigen or prostate specific antigen, as well as genes encoding HIV *env* proteins and hepatitis B surface antigen. (See page 50, lines 5-13)

With respect to treatment of cancer, the specification teaches administration of adenoviral vectors comprising genes including $p16^{b}$, $p21^{WAF1, CIP1, SDI1}$ and $p27^{KIP1}$ as well as other tumor suppressors such as RB, APC, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, zac1, p73, BRCA1, VHL, FCC, MMAC1, MCC, p16, p21, p57, C-CAM, p27 and BRCA2. The specification further teaches treatment of cancer by administration of adenoviral vectors comprising genes encoding inducers of apoptosis, such as Bax, Bak, Bcl-X_S, Bik, Bid, Harakiri, Ad E1B, Bad and ICE-CED3 proteases. (See page 46, lines 22-24) The specification also teaches that adenoviral vectors of the invention can comprise antisense nucleic acids which are complementary to the base sequences of oncogene-encoding DNA and RNA such as *ras, myc, neu, raf erb, src, fms, jun, trk ret, gsp, hst, bcl* and *abl*. (Page 48, lines 6-7)

Applicants' specification also enables those of skill in the art to practice administer adenoviral vectors by a variety of modes. Specifically, pages 72-74 of the disclosure teach

that the viral particles of the invention may be administered by a variety of therapeutic regimens so long as the target tissue is available via that route. Suitable routes include oral, nasal, buccal, rectal, vaginal and topical administration. The disclosure further teaches that administration can be by orthotopic, intradermal subcutaneous, intramuscular, intraperitoneal, or intravenous injection. Pharmaceutical compositions of the invention would normally include physiologically acceptable carriers, buffers or other excipients. The specification teaches that for application against tumors, direct intratumoral injection, injection of a resected tumor bed, regional (i.e., lymphatic) or general administration can be practiced as well as continuous perfusion over hours or days via a catheter to a disease site, e.g., a tumor or tumor site.

The disclosure teaches that the therapeutic compositions of the invention may be administered in the form of injectable compositions either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. These preparations also may be emulsified. A typical composition for such purpose comprises a pharmaceutically acceptable carrier such as human serum albumin in phosphate buffered saline. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oil and injectable organic esters such as ethyloleate. Aqueous carriers are disclosed as including water, alcoholic/aqueous solutions, saline solutions, parenteral vehicles such as sodium chloride, Ringer's dextrose and the like. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial agents, anti-oxidants, chelating agents and inert gases. The pH and exact concentration of the various components the pharmaceutical composition are adjusted according to well known parameters.

The specification also teaches formulations suitable for oral administration. Oral formulations include such typical excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. The compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders. When the route is topical, the form may be a cream, ointment, salve or spray. Those of skill in the art would appreciate that an effective amount of the therapeutic agent is determined based on the intended goal, for

example (i) inhibition of tumor cell proliferation, (ii) elimination or killing of tumor cells, (iii) vaccination, or (iv) gene transfer for long term expression of a therapeutic gene.

Applicants submit the declaration of Kerstin B. Menander, Ph.D., M.D. the Vice President of Clinical Development at Introgen Therapeutics ("Introgen") as evidence that the rejected claims are enabled (Appendix F). Dr. Menander's declaration sets forth the numerous clinical trials, involving Introgen's INGN 201 adenovirus-p53 composition, which is disclosed in the specification of the present application, that are underway or have recently been completed or that have been approved. The Declaration also sets forth a number of clinical trials that have employed another adenoviral p53 construct, Schering Plough's SCH 58500 adenovirus-p53 construct. It further describes the clinical trials of other researchers beyond the field of cancer therapeutics including for treatment of cystic fibrosis, partial ornithine transcarbamylase deficiency, Canavan Disease, Peripheral Vascular Disease, Critical Limb Ischemia, Diabetic Ulcers, Coronary Artery Disease, Peripheral Arterial Occlusive Disease, Hemophilia, Treatment of Dialysis Patients, and Parkinson's Disease.

Applicants further point to the U.S. Patent and Trademark Office's own training guide, albeit on utility instead of enablement, which states, "[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process for a therapeutic or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." MPEP 2107.03 IV. Because the requirements for utility and enablement are intertwined, Applicants contend that the submission of bountiful clinical trial evidence strongly weighs against a rejection for enablement. The clinical trial evidence shows that adenovirus-p53 is being tested against a number of cancers, including head and neck, non-small cell lung carcinoma, ovarian, breast, esophageal, lung, glioma, prostate, bladder, and solid tumors form colon cancer, breast cancer, prostate cancer, sarcomas, non-small cell lung carcinomas and head and neck cancer. This evidence further indicates that administration of Ad-p53 is achieved regionally, intravenously, directly, intraperitoneally, and intravesically. The Declaration of Dr. Menander confirms the enablement of the claimed invention. Applicants respectfully request that the rejection of the claims for lack of enablement be withdrawn in view of the following reasons.

H. The Anticipation Rejection over Zhang '010 Should be Withdrawn.

The anticipation rejection of all pending claims (70-226) over Zhang, U.S. Patent 6,410,010 should be withdrawn because Zhang fails to disclose element a) in each of amended independent claims 70, 101, 132, 163 and 194 which recite practice of a specific methodology for preparing a therapeutic adenovirus composition. Specifically, step a) calls for preparing a therapeutic adenovirus composition by a process that includes i) growing host cells in a media; ii) providing nutrients to said host cells; iii) infecting said host cells with an adenovirus; iv) lysing said host cells to provide a lysate; v) purifying adenovirus from said lysate to provide therapeutic adenovirus; vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition. Because, practice of this set of steps is nowhere disclosed in Zhang '010 the rejection under 35 U.S.C. §102 must be withdrawn. Not only are each of independent claims 70, 101, 132, 163 and 194 novel over Zhang '101 but each of dependent claims 71-100, 102-131, 133-162, 164-193 and 195-226 depending directly or indirectly therefrom are also novel. As such, the rejection under 35 U.S.C. §102(e) is improper and should be withdrawn.

I. The Rejection over Zhang '010 in combination with Shabram '520 Under 35 U.S.C. §103(a) Should be Withdrawn.

The Section 103 rejection of selected dependent claims (73-74, 77, 104-105, 108, 135-136, 139, 166-167, 170, 197-198 and 201) over Zhang '010 in combination with Shabram '520 should be withdrawn because there is no motivation to combine Shabram '520 with Zhang '010 and even if Shabram were so combined it would fail to make up for the deficiencies of Zhang in teaching the elements of the independent claims from which these claims depend. Shabram is cited as teaching that "unencapsulated adenovirus may be removed by Benzonase™ treatment but does not relate to the treatment of human subjects and would not be combined with Zhang '010. Moreover, Shabram fails to make up for the deficiencies in Zhang '010 with respect to teaching the methodology of step a) of Applicants' claims. Moreover, Shabram further fails to make up for the deficiencies of Zhang with respect to Applicants' dependent claims. Accordingly, the Section 103 rejection against 73-74, 77, 104-105, 108, 135-136, 139, 166-167, 170, 197-198 and 201 should be withdrawn.

CONCLUSION

In view of the above amendment, applicants believe the pending application is in condition for allowance.

Respectfully submitted,

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April 6, 2005